44. (Amended) A glycopeptide library according to claim 32, wherein the peptide scaffold is a [core protein] tandem repeat of MUC1.

REMARKS

Claims 1-44 are pending. Claims 33, 38 and 44 have been amended. Support for the amendments to claims 33 and 44 is found on page 11, lines 15-21. Claims 1-31, 39 and 41 have been withdrawn from consideration. Claims 1-44 remain in the case.

Claims 33, 38 and 44 are rejected under the second paragraph of Section 112. Claims 33 and 44 have been amended to refer to libraries built from a peptide scaffold that is a tandem repeat of MUC1. The term MUC1 has been retained in the claims, as it is the established name of these structures. See, for example, U.S. 5,989,552. However, the unabbreviated "mucin-1" has been added. Claim 38 has been amended to replace the term "antibody-like" with the term "antibody." Reconsideration and withdrawal of the rejection under the second paragraph of Section 112 is respectfully requested.

Claims 32, 34-38, 40, 42 and 43 are rejected under Section 102(a), or in the alternative under Section 103(a), based on Rao *et al.* (U.S. 5,795,958). Claims 32 and 34-38 are rejected under Section 102(b) or Section 103(a) based on Vetter (WO 95/18971). Claims 32-37 are rejected under Section 102(b) based on Frische *et al.* (abstract *J. Pept. Sci.*).

Each of the cited documents discloses collections of individually-synthesized glycopeptides. For example, while Rao *et al.* refers to "a collection or a library of peptide sequences to which a carbohydrate is covalently attached" (Rao at column 3, lines 15-17), each glycopeptide is individually synthesized using a multicolumn automated peptide synthesizer by sequentially coupling individual amino acids including pre-fucosylated serine, and subsequently combined to form the collection or library. Vetter *et al.* describes solid-phase methods of attaching carbohydrates (N-linked), through a linker arm, to solid

supports that have no structural definition, and serve solely as an anchor, having no part in the activity of the molecule. The solid support is typically a polymer. A single compound is produced in each reaction vessel, using a solid support. And Frische *et al.* describes the synthesis of a series of peptides and glycopeptides based on the sequence of mouse hemoglobin, through solid phase techniques. Preglycosylated serine and threonine are used. Each glycopeptide is separately synthesized, as in Rao and Vetter, and then combined to form a so-called "library."

In response, the examiner urges that "patentability of a product is based not on the process by which the product is made rather, whether the product has been established in the prior art." The examiner appears to be referring to MPEP §2113, which states that "the Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" (citing *In re Fessman*). However, MPEP §2113 also states that "once the Examiner provides ***a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art***, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product" citing *In re Marosi* (emphasis added). *In re Marosi* is the case cited by the examiner in the current action.

In the present situation, the manner of making the library precludes a "rationale" that the claimed product, applicant's library, is "the same or similar to that of the prior art." The prior art describes collections of individually-synthesized glycopeptides. For example, in Rao *et al.*, each glycopeptide is individually synthesized using a multicolumn automated peptide synthesizer by sequentially coupling individual amino acids including pre-fucosylated serine, and subsequently combined to form a relatively small collection or library. Rao does not disclose a combinatorially-generated library of randomly glycosylated structures, and it would be humanly impossible to individually synthesize all glycopeptides that would be contained in a combinatorially-generated library as presently claimed. Rao cannot possibly be alleged to disclose libraries that would have the size and diversity of the libraries claimed by applicants, and thus cannot reasonably be said to disclose a product that is the same or similar to applicant's claimed library.

A similar situation exists with respect to Vetter (WO 95/18971) and Frische *et al.* The collection of structures produced in Vetter all carry a single carbohydrate structure with no provision for further iterative synthesis leading to more complex structures, as in the randomly glycosylated libraries according to applicants' invention. Similarly to Rao, Vetter's solid-phase synthesis does not lead to large numbers of randomly-glycosylated structures, such as are contained in the combinatorially-generated libraries according to the present invention. Frische *et al.* describes the synthesis of a series of peptides and glycopeptides based on the sequence of mouse hemoglobin, through solid phase techniques. Preglycosylated serine and threonine are used. Each glycopeptide is separately synthesized, as in Rao and Vetter, and then combined to form a so-called "library." The arguments presented above with respect to Rao and Vetter apply with equal force to Vetter, and there is no reasonable basis for an assumption on the part of the Patent Office that the product described in Vetter or Frische is the same or similar to that claimed by applicant.

As a summary of the differences between the present invention and the disclosures of Rao, Vetter and Frische, applicants have prepare a comparison table which is appended hereto. The table clearly shows why none of the cited references anticipate or render obvious applicants' claims to a combinatorially-generated glycopeptide library, which has tremendous diversity. Diversity is important for the discovery of biologically active components. Applicants' glycopeptide libraries provide the necessary diversity, by using combinatorial methods in which several and various carbohydrates are randomly placed on a given sequence of amino acids. This approach greatly enhances the probability of discovering biologically active molecules.

The present invention provides a way of identifying patterns in protein glycosylations. Such information is needed in the discovery of antigens for immunotherapy of cancers, inhibitors of bacterial adhesion to prevent infections, inhibitor of cell-cell adhesion to prevent inflammations etc. Random and combinatorial approaches provide the only way to deal with millions of statistically possible ways of placing a variety of carbohydrate structures along a protein core. This approach offers a fast and powerful route to discover therapeutics. Mucins (MUC) are epithelial cell surface glycoproteins, the

core of which often is made of tandemly repeating short sequences. Most glycosylations are O-linked in nature, with serines and threonines being the most predominant amino acids. Being very large in size and length, the glycosylations extend far out on the epithelial cell surface and become the foremost contact points for a variety of functional molecules, antibodies, immune cells and even for infections by pathogens like bacteria and viruses. Knowledge of their glycosylation patterns is, therefore, important and challenging. In order to design competitive inhibitors and antigens, it is important to know the sites of glycosylations, as well as the nature and size of the carbohydrates at each site. If one considers the permutations and combinations that arise from all the unique sites and the variety of carbohydrates that may exist on the tandem repeat, the number of possible arrangements becomes unimaginably large. The true glycosylation pattern of a mucin tandem repeat can only be discovered through a combinatorial approach, *i.e.*, by randomly glycosylating and generating a near true diversity to enhance the possibility of locating a tandem repeat that has the glycosylation pattern similar to that of a mucin. Synthesis of a library of thousands of glycopeptides by employing automated solid phase techniques, as in Rao, Vetter or Frische, would not be feasible. While the screening process of pure individual compounds is simpler, their synthesis even with automation yields vastly restricted diversity. Combinatorial and random techniques, on the other hand, result in all of the statistically possible ways in which various reactants can combine without actually identifying any of them until a screening process detects a 'hit' for further analysis and identification.

To illustrate the point, consider the core proteins of mucins, which are rich in both glycosylation sites and carbohydrate diversity. The 17 amino acid tandem repeat of human intestinal mucin MUC3 contains 12 unique sites (serines and threonines) for glycosylation. If 3 different carbohydrate structures were to chemically link to a single tandem repeat of MUC3, it is theoretically possible to create a library of over 16 million different glycopeptides with different magnitudes of glycosylation. The single most powerful benefit of having all random combinations is the ability to locate a glycopeptide with the right glycosylation pattern that is characteristic of a cancer-associated mucin. This is not achieved or suggested by Rao, Vetter or Frische.

In view of the foregoing amendments and remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Rao (U.S. 5,795,958)	**Vetter (WO 95/18971)**	**Frische (*J. Pept. Sci.*)**	**Present invention (09/143,379)**
Limited collection (array) of individually-synthesized glycopeptides	Limited collection (array) of individually-synthesized glycopeptides	Limited collection (array) of individually-synthesized glycopeptides	Library of randomly-synthesized glycopeptides that contains all statistically possible variations of glyscosylation pattern
Quantities of glycopeptides are established at synthesis.	Quantities of glycopeptides are established at synthesis.	Quantities of glycopeptides are established at synthesis.	The glycopeptides are formed in a mixture of unknown quantities.
Identity of all glycopeptides in the collection is known at the outset.	Identity of all glycopeptides in the collection is known at the outset.	Identity of all glycopeptides in the collection is known at the outset.	Identity of the glycopeptides in the library is predictable, but is not known at the time of library synthesis.
When an active component is discovered its identity is instantly known, since all members of the array are made individually.	When an active component is discovered its identity is instantly known, since all members of the array are all made individually.	When an active component is discovered its identity is instantly known, since all members of the array are all made individually.	At the time the active component is discovered its identity is yet to be determined.

Rao (U.S. 5,795,958)	Vetter (WO 95/18971)	Frische (*J. Pept. Sci.*)	Present invention (09/143,379)
The number of glycopeptides in the collection is severely limited by the availability of glycosylated amino acids, which must be used to synthesize individual glycopeptides.	These are 'N-linked glyco-conjugates' without a peptide scaffold. These cannot be termed 'glycopeptides'.	This is a collection of individually synthesized glycopeptides. The synthesis uses pre-synthesized glycosylated amino acids, whose availability is restricted.	Easily accessible and simple glycosyl donors and glycosylation sites on a peptide scaffold create a very large number of glycopeptides.
This collection of glycopeptides is neither randomly nor combinatorially formed. They are all individually synthesized.	This collection of glycopeptides is neither randomly nor combinatorially formed. They are all individually synthesized.	This collection of glycopeptides is neither randomly nor combinatorially formed. They are all individually synthesized.	This library is formed by random and combinatorial reactions between glycosyl donors and glycosylation sites.
There is no mathematical expression to define the size of this library. In fact there is no need for a mathematical expression since they are all individually made.	There is no mathematical expression to define the size of this library. In fact there is no need for a mathematical expression since they are all individually made.	There is no mathematical expression to define the size of this library. In fact there is no need for a mathematical expression since they are all individually made.	The size of this library is defined by an expression $(x + 1)^n$, where 'x' is the number of glycosyl donors and 'n' is the number of glycosylation sites of the peptide scaffold.

Rao (U.S. 5,795,958)	Vetter (WO 95/18971)	Frische (*J. Pept. Sci.*)	Present invention (09/143,379)
The peptide scaffold and glycosylated amino acids may be varied in creating the collection of glycopeptides.	These is no peptide scaffold and no need for glycosylated amino acids.	Any peptide scaffold can be used, since they are all individually synthesized without random or combinatorial approach.	While there is no advantage in using more than one peptide scaffold at a time, multiple scaffolds may be used as a mixture.
It is humanly impossible to synthesize thousands of glycopeptides even by automated synthesizers. It will take years to create a large collection of glycopeptides, since all the glycosylated amino acids must be pre-synthesized.	It is humanly impossible to synthesize thousands of glycopeptides even by automated synthesizers. It will take years to create a large collection of glycopeptides, since all the glycosylated amino acids must be pre-synthesized.	It is humanly impossible to synthesize thousands of glycopeptides even by automated synthesizers. It will take years to create a large collection of glycopeptides, since all the glycosylated amino acids must be pre-synthesized.	Random and combinatorial reaction permits the formation of millions of glycopeptides in a single reaction, all in a matter of days.

Rao (U.S. 5,795,958)	Vetter (WO 95/18971)	Frische (*J. Pept. Sci.*)	Present invention (09/143,379)
This collection of glycopeptides severely limits the active component discovery due to its size and lack of random spatial arrangement of carbohydrate structures on a peptide scaffold.	'Active' components are N-linked glyco-conjugates and not glycopeptides.	Since the glycopeptides must be individually synthesised, there are severe limitations to the power and probability of discovery.	This random and combinatorial library offers tremendous power, both in numbers and diversity, for the discovery of an active component. Various isomeric glycopeptides of same molecular formula due to spatially arranged combinations of carbohydrates provides a unique property that provides several scaffold-dependent variations for a single carbohydrate structure or a combination of several different carbohydrate structures.